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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,253	FRANCIS-LANG ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2009 and 15 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8-10 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-10 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-9-2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on March 9, 2009 and May 15, 2009.

Currently, claims 1, 8-10, and 26 are pending and under examination on the merits in the instant case.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 103

Claims 1 and 8-10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Costa et al. and Liu et al. for the reasons of record as set forth in the Office action mailed on September 9, 2008 and for the reasons stated below.

Applicant's arguments filed on March 9, 2009 have been fully considered but they are not persuasive. Applicant asserts that the combination of Costa et al. and Liu et al. does not render

the claims obvious because one of ordinary skill in the art would not have been motivated to combine the references since Costa et al. fail to teach using a UP nucleic acid. First, it is noted that the *KSR* decision forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip. op at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR,* USPQ2d at 1396) (available at http://www.USPTO.gov/web/offices/dcom/bpai/prec/fd071925.pdf). Second, response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As set forth in the last Office action, the lack of UP in the reference of Costa et al. is taught by Liu et al. Third, contrary to applicant's assertion, one of ordinary skill in the art would have been sufficiently motivated to combine the teachings of Costa et al. and Liu et al., thereby arriving at the claimed invention, because Costa et al. clearly taught assay methods for identifying a candidate agent that modulates beta-catenin pathway that is implicated in cell proliferation and apoptosis (modifiers of beta-catenin (MBCAT)), especially of tumor cells, and because Liu et al. taught that UP is up-regulated in tumor cells and thus negatively modulating (inhibiting or blocking) UP activity by making an UP inhibitor candidate agent may provide cancer therapeutic approaches.

Applicant argues that there are "hundreds of genes implicated in cell proliferation" and thus one of ordinary skill in the art would not have a reason to pursue a UP nucleic acid in the method of identifying a candidate modulator of beta-catenin pathway. Applicant is correct that there are myriad genes implicated in cell proliferation. However, Costa et al. expressly taught that MBCAT can be identified by detecting "cell proliferation changes produced by the

originally identified candidate agent" by using cells of non-human animals "predetermined to have a disease or disorder implicating the beta-catenin pathway" such as cancer. See page 5, lines 9-16. Hence, Costa et al. clearly suggested to one of ordinary skill in the art that the potential MBCAT candidate agent can be more expeditiously identified by narrowing the pool of candidate agents to those that produce cell proliferation changes in cancer cells. At the time the invention was made, it was known in the art, since the year of 1998 when the Liu et al. reference was published, that UP activity is involved in cancer cell proliferation and that an inhibitor of UP, 5-benzylacyclouridine (BAU) had already undergone clinical trials for its ability to inhibit UP and its potential to treat cancer. As such, UP was an art-recognized cancer target gene worthy of clinical research, expenses, and time, and there were not "hundreds of genes implicated in cell proliferation" that were worthy of such involved investment in the art. Taken together, given the clinically validated finding that UP activity indeed produces cell proliferation changes in cancer cells and the specific teaching of Costa et al. that MBCAT is an agent that produces cell proliferation changes in cancer cells, one of ordinary skill in the art would have had a good and sufficient reason to pursue UP as a potential modulator of beta-catenin pathway that regulates cell proliferation of cancer cells.

Applicant further argues that the combination of Costa et al. and Liu et al. would not have led one of ordinary skill in the art to arrive at the claimed methods because neither of them recognized a nexus between UP and beta-catenin. First, it appears that applicant has misinterpreted the claimed methods. The claimed methods are screening methods for determining or identifying whether a "candidate test agent" is a "candidate beta-catenin pathway modulating agent" in an expression assay system that comprises a UP nucleic acid, wherein the "candidate test agent" is a nucleic acid modulator of UP. Thus, the claims are "testing" whether a

UP modulator is a "candidate" MBCAT, and therefore a pre-existing, already-verified nexus between UP and beta-catenin pathway is not required for one of ordinary skill in the art to arrive at the claimed invention. Since the claims are expression assay-based detection/screening/testing methods wherein UP inhibitor is a "candidate" for MBCAT, all that is required for one of ordinary skill in the art to arrive at the claimed methods is a reasonable degree of predictability that the cancer cell proliferation effects of UP may be related or associated with the cancer cell proliferation signaling activity of the beta-catenin pathway. In fact, the claimed methods clearly indicate that one can simply identify a candidate beta-catenin pathway modulating agent by contacting an expression assay system with a UP inhibitor agent and detecting differences between the UP inhibitor agent activity and the reference activity. See claim 1, steps (a)-(c), for example. There is no step whatsoever that requires one to know a UP inhibitor is a candidate beta-candidate pathway modulator prior to performing steps (a)-(c). As recited, identifying a UP inhibitor as a "candidate" beta-candidate pathway modulator is the end result obtained from testing the hypothesis that UP inhibitor may modulate beta-catenin pathway, which is reasonably formulated by combining the teachings of Costa et al. and Liu et al. for the reasons stated above. Further, applicant's attention is directed to the fact that "Obviousness does not require absolute predictability of success." See *In re O 'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988) at 903.

In view of the foregoing, it is concluded that applicant's arguments do not clearly point out the patentable novelty which he or she thinks in view of the state of the art disclosed by the references cited. Hence, this rejection is maintained.

New Objections/Rejections Necessitated by Amendment

Claim Objections

Claim 1 is objected to because the lines are crowded too closely together, making reading difficult. Note that the line spacing in lines 8-10 of claim 1 as currently filed is altered from as originally filed. Substitute claims with lines one and one-half or double spaced on good quality paper are required. See 37 CFR 1.52(b).

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Costa et al. (WO 03/052068 A2, applicant's citation) in view of Liu et al. (*Cancer Research,* 1998, 58:5418-5424, applicant's citation), and Elbashir et al. (*Methods,* 2002, 26:199-213).

The claims are drawn to a method of identifying a candidate beta-catenin pathway modulating agent, comprising providing a candidate test agent siRNA targeted to uridine phosphorylase (UP) to an assay system and detecting the difference between the tested sample and the control (reference) sample in the assay system.

Costa et al. teach a method of identifying a candidate beta-catenin pathway modulating agent, comprising providing an MBCAT oligonucleotide such as an antisense oligonucleotide that modifies beta-catenin to an assay system and detecting the difference between the tested sample and the control (reference) sample in the assay system. They teach that the assay system is a cell proliferation assay or expression analysis because beta-catenin signaling pathway is implicated in cell proliferation and apoptosis, especially in relation to tumor cells. They teach that one can also identify a modifier of beta-catenin by performing *C. elegans* or other animal

mutant screening and identifying human orthologs/homologs by BLAST analysis. See pages 14-15, 20-26, 33-37, 41-42; claims 1 and 8-10. Costa et al. do not teach that the candidate test agent is an siRNA targeted to UP.

Liu et al. teach that human uridine phosphorylase (UP) activity is up-regulated in tumor tissues compared to normal tissues and suggest that blocking the UP activity may provide strategies for treating tumors. See the entire reference including Figure 6.

Elbashir et al. teach that siRNAs are a useful research and assay tool for studying and analyzing gene functions in cell biology or metabolic pathways because they mediate sequence-specific inhibition of target gene in cultured mammalian cells.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to fully utilize the teachings and guidelines of Costa et al. as to how to identify a candidate agent that modulates beta-catenin signaling pathway, which would have led the skilled artisan to make and use an siRNA targeted to UP as the candidate agent.

One of ordinary skill in the art would have been motivated to make the claimed invention because Costa et al. explicitly taught the method of identifying a candidate beta-catenin pathway modulating agent comprising an antisense oligonucleotide against a beta-catenin modifier gene. Since Costa et al. provided detailed guidelines and methodologies as to how to identify a beta-catenin modifier gene, and since UP activity was known to be significantly elevated in tumor cells compared to normal cells and was therefore implicated in cell proliferation as taught by Liu et al., one of ordinary skill in the art would have been motivated to test whether the cancer cell proliferative activity of UP is related to the cancer cell proliferation signaling of the beta-catenin pathway by making an inhibitor against UP and detect changes in an expression assay system. Since Costa et al. taught that an MBCAT oligonucleotide such as antisense oligonucleotide is

useful as the candidate test agent, and since antisense oligonucleotides and siRNAs are functionally equivalent such that both inhibit target gene expression/activity in a sequence-specific manner, and since Elbahsir et al. clearly taught that one can make and use a target-specific siRNA in mammalian cell culture systems for assay or research purpose, one of ordinary skill in the art would have reasonably made an siRNA targeted to UP and used it as a candidate test agent in the method of identifying a candidate MBCAT of Costa et al. Since the knowledge and skills required to arrive at the claimed invention were within the technical grasp of one of ordinary skill in the art, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner, Art Unit 1635